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<b>(51) International Patent Classification<sup>5</sup> :</b> <b>A61K 7/06</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/27563</b> <b>(43) International Publication Date:</b> 8 December 1994 (08.12.94)
<b>(21) International Application Number:</b> PCT/US94/05361 <b>(22) International Filing Date:</b> 16 May 1994 (16.05.94) <b>(30) Priority Data:</b> 068,256 28 May 1993 (28.05.93) US  <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 068,256 (CON) Filed on 28 May 1993 (28.05.93)  <b>(71) Applicant (for all designated States except US):</b> HANDEL- MAN, Joseph, H. [US/US]; 26 West 61st Street, New York, NY 10023 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> AHLUWALIA, Gurpreet, S. [US/US]; 8632 Stable View Court, Gaithersburg, MD 20879 (US). SHANDER, Douglas [US/US]; 16112 Howard Landing Drive, Gaithersburg, MD 20878 (US).  <b>(74) Agents:</b> GALLOWAY, Peter, D. et al.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US).		<b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> INHIBITION OF HAIR GROWTH  <b>(57) Abstract</b>  Mammalian hair growth is reduced by applying to the skin a composition including an inhibitor of 5-lipoxygenase.		

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### INHIBITION OF HAIR GROWTH

The invention relates to the inhibition of hair growth.

Arachidonic acid is released from  
5 membrane lipids in response to injury or other  
irritation. The enzyme 5-lipoxygenase converts  
arachidonic acid into 5-hydroperoxyerco-  
6,8,11,14-tetraenoic acid, which subsequently is  
converted into a family of compounds known as  
10 leukotrienes. The exact biological role of  
leukotrienes has not yet been determined.

It has now been found that mammalian  
(including human) hair growth can be inhibited  
by applying to the skin a composition including  
15 an inhibitor of 5-lipoxygenase in an amount  
effective to reduce hair growth in the applied  
area.

Examples of 5-lipoxygenase inhibitors  
that have been found effective in reducing hair  
20 growth include quercetin (3,3',4',5,7-  
pentahydroxy flavone), dl- $\alpha$ -tocopherol, apigenin  
(4',5,7-trihydroxy flavone), propyl gallate,  
NDGA (nondihydroguaianetic acid), and caffeic  
acid (3,4-dihydroxycinnamic acid). All of these  
25 compounds are known in the art and are  
commercially available. Other inhibitors of 5-  
lipoxygenase are known in the art; see, for

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example, Laughton et al., 42 Biochemical Pharmacology 1673 (1991).

5 The composition preferably includes a non-toxic dermatologically acceptable vehicle or carrier which is adapted to be spread upon the skin. Examples of suitable vehicles are acetone, alcohols, or a cream, lotion, or gel which can effectively deliver the active compound. In addition, a penetration enhancer  
10 may be added to the vehicle to further enhance the effectiveness of the formulation.

The concentration of the inhibitor in the composition may be varied over a wide range up to a saturated solution, preferably from 1 to  
15 30% by weight or even more; the reduction of hair growth increases as the amount of inhibitor applied increases per unit area of skin. The maximum amount effectively applied is limited only by the rate at which the inhibitor  
20 penetrates the skin. Generally, the effective amounts range from 100 to 3000 micrograms or more per square centimeter of skin.

The composition should be applied to the area of the body where it is desired to  
25 inhibit hair growth. Typically, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, and chin. The composition can also be applied to the legs, arms, torso or armpit.  
30 The composition is particularly suitable for the treatment of hirsutism. In humans, the composition should be applied once or twice a day, or even more frequently, for at least three months to achieve a perceived reduction in hair  
35 growth.

Reduction of hair growth is demonstrated when the frequency of hair removal

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is reduced, or the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed by shaving (i.e., hair mass) is reduced. Male intact Golden Syrian hamsters are considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster.

To evaluate the effectiveness of a particular inhibitor, the flank organs of each of a group of hamsters are depilated by applying a thioglycolate based chemical depilatory (Surgex). To one organ of each animal 10-25  $\mu$ l. of vehicle alone once a day is applied, while to the other organ of each animal an equal amount of vehicle containing the 5-lipoxygenase inhibitor is applied. After thirteen applications (one application per day for five days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair growth is calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

The preferred 5-lipoxygenase inhibitors were tested according to the above procedure; the results are presented in Table 1. Vehicle A is acetone; vehicle B is 35% dipropylene glycol, 30% ethanol, 25% acetone, and 10% benzyl alcohol; vehicle C is 68%

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purified water, 16% ethanol (200 proof), 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol, and 2% propylene carbonate; vehicle D is 80% ethanol (190 proof), 17.5%

- 5 purified water, 2% propylene glycol dipelargonate, and 0.5% propylene glycol; and vehicle E is a moisturizing lotion containing common cosmetic ingredients which include emulsifiers, detergents and preservatives.

Table 1

<u>Compound</u>	<u>Dose</u>	<u>Vehicle</u>	<u>pH</u>	<u>HAIR MASS</u>		<u>Percent Inhibition</u>
				<u>Treated</u> (mg)	<u>Control</u> (mg)	
Quercetin	5%	A	6.0	1.100±.10	1.543±.10	27±6
	10%	B	5.5	0.419±.07	2.679±.22	83±4
dl- $\alpha$ -Tocopherol	5%	A	5.0	0.400±.06	0.846±.10	49±7
	5%	C	10.0	1.019±.22	2.230±.26	54±9
Apigenin	10%	D	8.0	0.271±.0.09	1.380±0.22	82±5
	5%	D	7.0	0.870±.15	2.553±.16	67±5
	10%	D	6.5	0.450±.11	2.391±.21	81±4
	5%	D	6.0	1.740±.06	2.424±.17	26±5
Propyl gallate	15%	E	4.0	0.797±.13	2.148±.22	62±7
NDGA						
Caffeic acid						

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It will be appreciated by those skilled in the art that the invention can be performed within a wide range of equivalent parameters of composition and conditions without  
5 departing from the spirit or scope of the invention or of any embodiment thereof.

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C L A I M S

1. A process of inhibiting mammalian hair growth, comprising applying to the skin a composition including an inhibitor of 5-lipoxygenase in an amount effective to reduce hair growth.
2. The process of claim 1, wherein said inhibitor is quercetin.
3. The process of claim 1, wherein said inhibitor is dl- $\alpha$ -tocopherol.
4. The process of claim 1, wherein said inhibitor is apigenin.
5. The process of claim 1, wherein said inhibitor is propyl gallate.
6. The process of claim 1, wherein said inhibitor is NDGA.
7. The process of claim 1, wherein said inhibitor is caffeic acid.
8. The process of claim 1, wherein said concentration of said inhibitor in said composition is between 1% and 30%.
9. The process of claim 1, wherein the composition is applied to the skin in an amount of from 100 to 3000 micrograms of said inhibitor per square centimeter of skin.
10. The process of claim 1, wherein the composition is applied to the skin on the face of said mammal.
11. A method of producing a composition for inhibiting mammalian hair growth, which comprises selecting an inhibitor of 5-lipoxygenase, and combining said inhibitor, in an amount effective to reduce hair growth, with a non-toxic, dermatologically acceptable vehicle or carrier.
12. A method according to claim 11, wherein said vehicle or carrier is adapted to be

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spread upon the skin of a mammal.

13. A method according to claim 11, wherein said inhibitor is as defined in any one of claims 2 to 8.

5 14. The new use of an inhibitor of 5-lipoxygenase for reducing hair growth.

15. A composition when used for inhibiting mammalian hair growth, which includes an inhibitor of 5-lipoxygenase in an amount  
10 effective to reduce hair growth and a non-toxic, dermatologically acceptable vehicle or carrier.

16. A composition according to claim 15, wherein said inhibitor is as defined in any one of claims 2 to 8.

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 5 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 13, no. 308 (C-617) & JP,A,01 196 126 (KAO CORP.) 14 April 1989 see abstract ---	1,2,8-16
A	US,A,4 530 844 (EMERBECK ET AL.) 23 July 1985 see the whole document ---	1-3,6, 8-16
A	DATABASE WPI Week 8441, Derwent Publications Ltd., London, GB; AN 84-254475 & JP,A,59 155 314 (RIKAGAKU KENKYUSHO) 4 September 1984 see abstract --- -/-	1,7-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

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Date of the actual completion of the international search

29 September 1994

Date of mailing of the international search report

10.10.94

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>S.T.N., File Supplier, Karlsruhe, DE, File            Chemical Abstracts, vol 101, n 2087            see the abstract            -----</p>	1,5,8-16

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/05361

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1, 8-16  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
The inhibition of 5-lipoxygenase is a property of many compounds. Due to the broadness of claim 1, the search has been carried out and based on the examples.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
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4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**LOCATION**      **PLACEMENT NO**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4530844	23-07-85	CA-A- 1240931 US-A- 4568696	23-08-88 04-02-86
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